REMARKS

Claims 1-19 are pending and under consideration in the instant Application. With the instant Amendment, Claims 1 and 6-9 are amended. A marked up version of amended paragraphs is attached hereto as Exhibit A. A marked up version of amended Claims 1 and 6-9 is attached hereto as Exhibit B. For the PTO's convenience, a clean copy of pending claims after entry of the instant amendment is attached hereto as Exhibit C.

Applicants reserve the right to prosecute any canceled subject matter in one or more continuation, divisional or continuation-in-part applications.

I. THE AMENDMENT OF THE SPECIFICATION

The specification has been amended on page 14 to correct a minor error in the nomenclature of the nucleic acid region. This amendment is supported by the specification as originally filed, for example, at pages 19, 25 and Figures 1 and 2. The specification has also been amended on page 47 merely to capitalize TRITON X-100 and to provide a generic name for TRITON X-100. As the amendments to the specification are fully supported by the specification as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested.

II. THE AMENDMENT OF THE CLAIMS

Claim 1 has been amended to recite, in relevant part, a method for the detection of a nucleic acid comprising using two primers and a probe with a binding sequence D which can bind to a sequence B and detecting the formation of a hybrid of the amplificate and probe, wherein the sequence between the binding sequences A and C contains no nucleotides that do not belong to a sequence E of the amplificate that is bound by binding sequence D of the probe and the amplificate does not exceed a total length of 100 nucleotides. Support for the amendment to Claim 1 can be found in Claim 1 as originally filed and in the specification, for example, at pages 26-27 and in Figures 1-3.

Applicants have amended Claims 6-9 without narrowing their scope merely to correct minor typographical errors.

As the amendments are fully supported by the specification as originally filed, they do not constitute new matter. Applicants hereby request entry of the Amendment to the Claims into the record.

III. THE OBJECTION TO THE SPECIFICATION

The specification stands objected to because the term TRITON X-100 allegedly should be capitalized and should be accompanied by generic terminology. Applicants submit that upon entry of the instant amendment the term TRITON X-100 is properly capitalized and accompanied by generic terminology. Applicants respectfully request that the objection to the specification be withdrawn.

IV. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-19 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. The PTO recognizes that the specification is enabling for the method of Claim 1 applied to a nucleic acid derived from isolated HCV RNA from human plasma. However, the PTO alleges that the specification does not provide enablement for the simultaneous detection of a number of nucleic acids, for the use of conditions such that non-specific hybridization reaction products are realized or for the use of primers of any length or the generation of an amplification product of any length. Applicants respectfully traverse the rejection on the grounds that the specification as originally filed fully enables one of skill in the art to use the method of Claims 1-19 with no undue experimentation.

A claim is enabled if one of skill in the art, guided by Applicant's disclosure, can make and use the claimed invention without undue experimentation. *See Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is not undue. *See In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985). While Applicants are required to provide an enabling disclosure, the disclosure is not required to teach, "and *preferably omits*, what is well known in the art." *See* M.P.E.P. § 2164.01 (emphasis added); *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986); *Lindemann Maschinen Fabrik v. American Hoist & Derrick*, 221 USPQ 481, 489 (Fed.

Cir. 1984). Among the factors to be considered when determining whether the necessary experimentation is undue are the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See In re Wands*, 8 U.S.P.Q.2d at 1404. In rejecting a claim for lack of enablement, the Examiner should cite any of these factors that are relevant, and specific technical reasons are *always required*. *See* M.P.E.P. at §§ 2164.01(a) 2164.04; *In re Wands*, 8 U.S.P.Q.2d at 1404.

Applicants submit that the specification fully enables one of skill in the art to make and use the full scope of Claims 1-19. Claims 1 and 16 each recite a method of detecting a nucleic acid. In each method, a plurality of amplificates is produced from a section of the nucleic acid with the aid of two primers. The amplificates are contacted with a probe having a binding sequence which can bind to a sequence located between the binding sequences of the primers or to the complement thereof. In each method, the formation of a hybrid of the amplificate and probe is detected. Significantly, the amplificate does not exceed a total length of 100 nucleotides. Claims 2-15 depend from Claim 1, and Claims 17-19 depend from Claim 16.

A. The PTO Has Provided No Evidence to Support the Quantity of Experimentation Necessary

As stated in *In re Wands*, specific technical reasons are always required to support the PTO's assertions in an enablement rejection. However, the PTO simply states that several man-years of experimentation are required to make and use the invention with no technical reasons provided at all. Applicants submit that, in the absence of specific technical reasons to support the PTO's position, the specification enables one of skill in the art to practice the invention with no undue experimentation.

B. The Amount of Direction or Guidance is not Limited to HCV RNA and Several Working Examples are Provided

The PTO incorrectly alleges that the amount of guidance provided in the specification is limited to HCV RNA isolated from human plasma. Applicants respectfully submit that the PTO has not correctly read the specification. First, the specification, for example at pages 13-27, teaches the application of the invention to any nucleic acid sample. The PTO has not provided any evidence or technical reasons, required by *In re Wands*, above, suggesting that the teaching of the specification would require any undue experimentation for application to any nucleic acid. Second, the specification provides detailed working examples for the detection of a variety of nucleic acids with the methods of the invention. For instance, in addition to the HCV RNA working example (*see* Example 1 at pages 47-50), the specification provides working examples for the detection of human genomic DNA, HIV RNA, HBV DNA and chlamydia DNA (*see* Examples 3 and 4 at pages 52-53 of the specification).

Applicants respectfully submit that the specification provides teaching sufficient to guide one of skill in the art to practice the invention with any nucleic acid and further provides several working examples that demonstrate the use of the invention with human, viral and bacterial nucleic acids.

C. Given the State of the Prior Art, Nucleic Acid Hybridization Conditions Can Be Determined by Routine Experimentation

The PTO contends that issues confront hybridization reactions and that there is a limit to which primers can be synthesized.

First, Applicants submit that nucleic acid hybridization reactions are routine in the art as indicated by the teaching of the specification and the references incorporated therein. Although several factors might affect the extent and specificity of hybridization as noted by the PTO, these factors are well known to one of skill in the art. In fact, the relationship between the melting point of any duplex and the factors influencing hybridization have been reduced to simple formulae. *See* Ausubel *et al.*, 1989, *Current Protocols in Molecular Biology*, Greene Publishing Associates and Wiley Interscience, NY, at pages 2.10.8-9; Meinkoth and Wahl, 1984, *Anal Biochem* 138:267-284. For instance, the melting temperature ("T_m") of a DNA-DNA duplex (longer than about 50 base pairs) in a pH range from pH 5 to 9, can be calculated according to the following formula:

T_m (°C) = 81.5 °C + 16.6(log molarity of monovalent cations) + 0.41(%C+G content of hybrid) - 0.61(% formamide) - 500/(length of hybrid in base pairs) - (% mismatched nucleotides in hybrid) *See* Ausubel at page 2.10.8; Meinkoth at 269.

For shorter sequences and for immobilized DNA, the formula is: T_m (°C) = 4(G+C) + 2(A+T), where G, C, A and T indicate the number of the corresponding nucleotide in the oligomer. *See* Meinkoth at 269. Similar formulae can be found for RNA-DNA hybrids (Ausubel at pages 2.10.8). Applicants submit that given the state of the prior art, one of skill is fully enabled to design or select primers, probes and hybridization conditions to carry out the methods of the invention with full regard to the issues confronting hybridization reactions noted by the PTO.

Furthermore, the specification provides exemplary hybridization conditions and detailed working examples demonstrating the use of the methods of the invention with a variety of nucleic acids. For instance, the specification teaches the design or selection of primers (*see, e.g.* pages 21-22) and the amplification of a nucleic acid (*see, e.g.* pages 28-31) including exemplary amplification conditions. The specification also teaches the design or selection of probes (*see, e.g.* pages 22-25) and the hybridization of the probe to a template (*see, e.g.* pages 31-33) including exemplary hybridization conditions. In addition, the specification provides detailed working examples (*see, e.g.*, Examples 1, 3 and 4) providing exemplary primers, amplification conditions, probes and hybridization conditions for a range of nucleic acids including human, viral and bacterial nucleic acids. Applicants submit that one of skill in the art, guided by the art and the specification, can practice the amplification and hybridization steps of the invention without undue experimentation.

Second, Applicants simply do not understand the PTO's contention that Applicants are claiming a product that would be the result of any number of oligonucleotide synthesis couplings. First, Claims 1-19 recite *methods* of using primers and probes. Second, the preparation of these primers and probes are well within the abilities of those of skill in the art. As discussed in the specification, the primers and probes can be made, for example, through routine synthetic techniques. Furthermore, the total length of the amplificate used in Claims

1-19 does not exceed 100 nucleotides. The PTO has provided no specific technical reasons that the preparation of primers or a probe for an amplificate that does not exceed 100 nucleotides would require undue experimentation.

D. The Specification Enables the Full Scope of Claims 1-19

The PTO alleges that the claims encompass the detection of any number of nucleic acid sequences and that conditions wherein highly non-complementary sequences are used in an amplification assay would yield meaningless results.

As discussed above, Applicants respectfully submit that the specification and prior art provide ample guidance to one of skill in the art to design or select primers, amplification conditions, a probe and hybridization conditions. The specification even provides guidance to one of skill in the art for conducting the methods of the invention in conditions when one or more of the primers or probe hybridize non-specifically to a nucleic acid while yielding meaningful results. At pages 41-42, the specification specifically addresses the concerns of the PTO. At page 41, the specification discusses the practice of the invention wherein one of the primers or probe hybridize non-specifically. At page 42, the specification even discusses the practice of the invention wherein all three of the primers and probe hybridize non-specifically.

Given such detailed teaching in the specification, Applicants submit that one of skill in the art could readily practice the methods of the present invention with multiple nucleic acids and potential non-specific hybridization with no undue experimentation.

E. Conclusion

As discussed above, the specification and the state of the prior art address each of the PTO's concerns with the enablement of Claims 1-19. Applicants respectfully request that the rejection of Claims 1-19 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-15 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The PTO asserts that Claim 1 is indefinite with respect to "essentially complimentary." Further, the PTO alleges that there is insufficient antecedent basis for the

limitation "the sequence region E" in Claim 1. Applicants submit that amended Claims 1-15 are definite and have proper antecedent basis.

First, the PTO alleges that Claim 1 is indefinite with respect to the term "essentially complimentary." Applicants submit that Claim 1, and hence dependent Claims 2-15, are definite with respect to what constitutes the metes and bounds of "essentially complimentary."

Under 35 U.S. C. § 112, second paragraph, the "specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." The "claims must have a clear and definite meaning when construed in light of the *complete patent document*." *Standard Oil Co. v. American Cyanamid Co.*, 227 USPQ 293, 296 (Fed. Cir. 1985) (emphasis added). "Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . . If the claims read in light of the specification reasonably apprize those skilled in the art of the scope of the invention, § 112 demands no more." *Personalized Media Communications, LLC v. U.S. Int'l Trade Comm'n*, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998); *see also Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994).

Page 25 of the specification provides a description of the term "essentially complimentary" sufficient to allow one of skill in the art to understand the bounds of the claims. In particular, the term essentially complementary indicates that the base pairs of a primer or probe are selected so that hybridization can occur under assay conditions or so that a primer extension reaction can proceed. The selection of the base pairs of the primer or probe and the hybridization or amplification conditions are well within the skill of those in the art, as discussed above. Applicants submit that the term "essentially complimentary," when construed in light of this definition, has a clear and definite meaning because one skilled in the art would understand the metes and bounds of the term.

Second, the PTO alleges that Claims 1-15 lack proper antecedent basis. Applicants submit that amended Claim 1 has proper antecedent basis and that Claims 2-15 depend from Claim 1.

Applicants therefore request that the PTO withdraw its rejection of Claims 1-15 under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Applicants submit that Claims 1-19 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-19 to issuance is therefore kindly solicited.

No fees in addition to the petition fee are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds U.S. Deposit Account No. 16-1150.

Respectfully submitted,

Date: 7/11/02

42,983

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Exhibit A
Marked Up Version of Amended Paragraphs

Please amend the specification as follows:

On Page 14 please amend the paragraph beginning "Fig. 4 shows sequences . . ." as follows:

Fig. 4 shows sequences of the utilized regions [i.e. A', B and C] *i.e.*, A', B and C'.

On page 47 please replace the paragraph beginning "**2.** add 500 μl lysis buffer..." with the following paragraph:

2. add 500 μl lysis buffer (incl. 1 μg carier-RNA (polyA) / ml : 5.4 M guanidinium thiocyanate; 10 mM urea; 10 mM Tris-HCL; 20 % [Triton X 100] TRITON X 100, (t-Octylphenoxypolyethoxyethanol; Polyethylene glycol tert-octylphenyl ether) pH 4.4

Exhibit B

Marked-Up Version of Amended Claims

1. (Twice amended) A method for the detection of a nucleic acid comprising [the steps]:

(a)- producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which can bind to a binding sequence [(A)] A of one strand of the nucleic acid and the other can bind to a binding sequence C' which is essentially complementary to a sequence C which is located in the 3' direction from A and does not overlap A[,]; and

(b)- contacting the amplificates with a probe having a binding sequence D which can bind to a sequence B located between the sequences A and C or to the complement thereof[,] ; and

(c)- detecting the formation of a hybrid of the amplificate and probe, wherein the sequence [located] between the binding sequences A and C contains no nucleotides that do not belong to [the] a sequence [region] E [formed from the binding sequence D of the probe and the sequence] of the amplificate [bound thereto] that is bound by binding sequence D of the probe and the amplificate does not exceed a total length of 100 nucleotides.

6. (Twice Amended) The method of claim 1, wherein at least one of the primers is [immobilizably-labelled] immobilizably-labeled and the probe is [detectably-labelled] detectably-labeled.

7. (Twice Amended) The method of claim 1, wherein at least one of the primers is [detectably-labelled] detectably-labeled and the probe is [immobilizably-labelled] immobilizably-labeled or is immobilized.

8. (Twice Amended) The method of claim 1, wherein the probe is [labelled] labeled with a fluorescence quencher as well as with a fluorescent dye.

9. (Twice Amended) The method of claim 1, wherein one of the primers [labelled] labeled with a first energy transfer component and the probe is [labelled] labeled with a second energy transfer component which is different from the first energy transfer component.

Exhibit C

Pending Claims After Entry of Instant Amendment

1. (Twice amended) A method for the detection of a nucleic acid comprising:

   (a)- producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which can bind to a binding sequence A of one strand of the nucleic acid and the other can bind to a binding sequence C' which is essentially complementary to a sequence C which is located in the 3' direction from A and does not overlap A; and

   (b)- contacting the amplificates with a probe having a binding sequence D which can bind to a sequence B located between the sequences A and C or to the complement thereof; and

   (c)- detecting the formation of a hybrid of the amplificate and probe, wherein the sequence between the binding sequences A and C contains no nucleotides that do not belong to a sequence E of the amplificate that is bound by binding sequence D of the probe and the amplificate does not exceed a total length of 100 nucleotides.

2. (Amended) The method of claim 1, wherein the binding sequence D of the probe overlaps one or both binding sequences of the primers.

3. (Amended) The method of claim 1, wherein at least one of the primers has nucleotides in its non-extendible part which do not hybridize directly with the nucleic acid to be detected or with its complement.

4. (Amended) The method of claim 1, wherein at least one of the binding sequences is not specific for the nucleic acid to be detected.

5. (Amended) The method of claim 1, wherein the total length of the amplificates does not exceed 61 nucleotides.

6. (Twice Amended) The method of claim 1, wherein at least one of the primers is immobilizably-labeled and the probe is detectably-labeled.

7. (Twice Amended) The method of claim 1, wherein at least one of the primers is detectably-labeled and the probe is immobilizably-labeled or is immobilized.

8. (Twice Amended) The method of claim 1, wherein the probe is labeled with a fluorescence quencher as well as with a fluorescent dye.

9. (Twice Amended) The method of claim 1, wherein one of the primers labeled with a first energy transfer component and the probe is labeled with a second energy transfer component which is different from the first energy transfer component.

10. (Amended) The method of claim 1, wherein the amplificate is detected by physical and/or spectroscopic methods.

11. (Amended) The method of claim 1, wherein at least one of the primers is not specific for the nucleic acid to be detected.

12. (Amended) The method of claim 11, wherein two of the primers are not specific for the nucleic acid to be detected.

13. (Amended) The method of claim 11, wherein the probe is not specific for the nucleic acid to be detected.

14. (Amended) The method of claim 1, wherein nucleotides which are each complementary to A, G, C and T are used in the amplification.

15. (Amended) The method of claim 1, wherein the amplificates are detected by means of mass spectroscopy.

16. (Amended) A method for the specific detection of a nucleic acid comprising the steps:

(a) - producing a plurality of amplificates of a section of the nucleic acid with the aid of at least two primers,

(b) - contacting the amplificates with a probe which can bind to the amplificate, and

(c) - detecting the formation of a hybrid of the amplificate and the probe,

wherein at least one of the primers is not specific for the group of organisms to which the organism to be detected belongs and the total length of the amplificate does not exceed 100 base pairs.

17. (Amended) The method of claim 16, wherein two of the primers are not specific for the nucleic acid to be detected.

18. (Amended) The method of claim 16, wherein the probe is not specific for the nucleic acid to be detected.

19. (Amended) The method of claim 16, wherein nucleotides which are each complementary to A, G, C and T are used in the amplification.